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International application number: PCT/GB05/001031

International filing date: 17 March 2005 (17.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: GB
Number: 0418556.7
Filing date: 19 August 2004 (19.08.2004)

Date of receipt at the International Bureau: 21 April 2005 (21.04.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

The Patent Office
Concept House
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Newport
South Wales
NP10 8QQ

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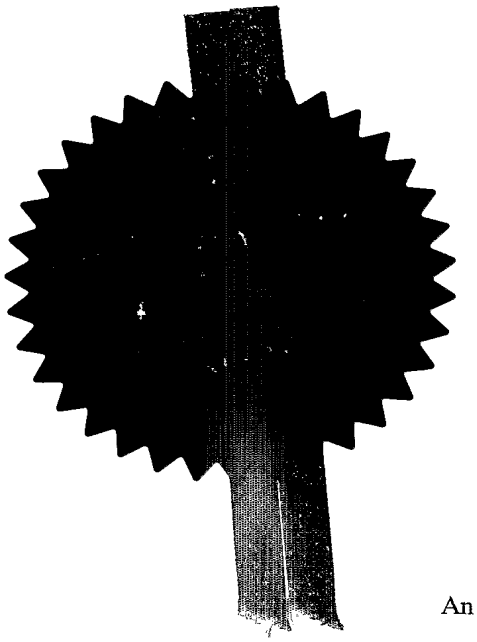

Signed William Morell

Dated 7 April 2005

Patents Form 1/77

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

20AUG04 E920215-7 D02090
P01/7700 0.00-0418556.7 CHEQUE

1. Your reference — REP07786GB

2. Patent application number *(The Patent Office will fill this part in)* — 0418556.7

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

   Arakis Ltd.
   Chesterford Research Park
   Little Chesterford
   Saffron Walden
   Essex
   CB10 1LX

   Patents ADP number *(if you know it)* 8306128001

   If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — The treatment of pain

5. Name of your agent *(if you have one)* — Gill Jennings & Every

   "Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

   Broadgate House
   7 Eldon Street
   London
   EC2M 7LH

   Patents ADP number *(if you know it)* — 745002

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

	Number of earlier UK application	Date of filing *(day / month / year)*

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request? — YES

   Answer YES if:
   a) any applicant named in part 3 is not an inventor, or
   b) there is an inventor who is not named as an applicant, or
   c) any named applicant is a corporate body.

   Otherwise answer NO (See note d)

Patents Form 1/77

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form	
Description	3 ✓ CF
Claim(s)	2 ✓
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	
Request for a preliminary examination and search (Patents Form 9/77)	
Request for a substantive examination (Patents Form 10/77)	NO
Any other documents (please specify)	

11. I/We request the grant of a patent on the basis of this application.

For the applicant
Gill Jennings & Every

Signature

Date 19 August 2004

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

PERRY, Robert Edward
020 7377 1377

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Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered YES in part 8, a Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

f) Part 7 should only be completed when a divisional application is being made under section 15(4), or when an application is being made under section 8(3), 12(6) or 37(4) following an entitlement dispute. By completing part 7 you are requesting that this application takes the same filing date as an earlier UK application. If you want the new application to have the same priority date(s) as the earlier UK application, you should also complete part 6 with the priority details.

The treatment of pain

Field of the invention

This invention relates to the treatment of pain

Background

Phenyl substituted beta-amino alcohols (I) are known to have antihypertensive, vasodilator, sympathomimetic, bronchodilator or cardiostimulant activity through agonism and antagonism at alpha and beta adrenoceptors.

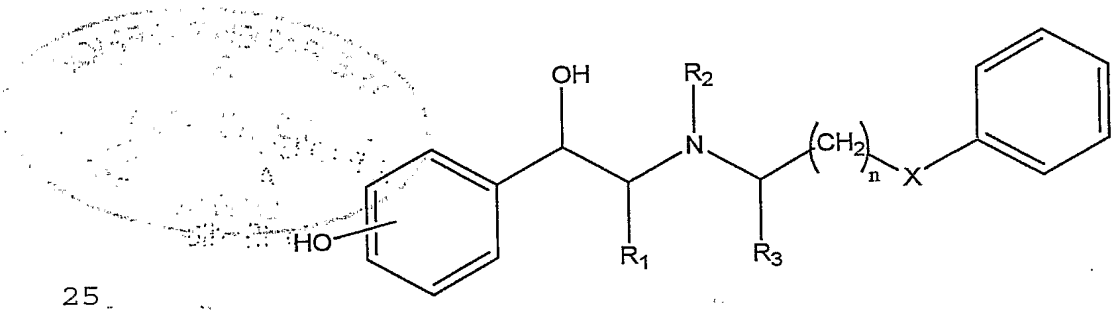
In GB Application No. 0406016.6 we have reported the cytokine modulating activity of these compounds, which is not dependant on the alpha and beta agonist or antagonist activity.

Summary of invention

Surprisingly it has been found that phenyl substituted beta-amino alcohols (I) work at reducing pain in pain conditions where cytokines are involved. According to the present invention, pain such as acute, chronic or neuropathic pain (including, but not limited to, pain associated with cancer, surgery, arthritis, dental surgery, painful neuropathies, trauma, musculo-skeletal injury or disease, and visceral diseases) and migraine headache in mammals, can be treated by the use of phenyl substituted beta-amino alcohols (I).

Description of Preferred Embodiments

Phenyl substituted beta-amino alcohols refer to compounds of general formula (I)



(I)

Wherein:

R_1 may be H or Me

R_2 may be H or alkyl and can be part of a ring with R_3

R_3 may be H or Me or CH_2 (when forming part of a ring with R_2)

n=0-2

X may be CH_2 or O

The two phenyl groups may be optionally substituted with OH, OMe, halogen, NHCHO, $NHSO_2Me$, $CONH_2$, SOMe

It is understood that the invention refers to salts, e.g. the hydrochloride, metabolites and pro-drugs thereof, as well as any diastereomers and enantiomers of (I).

Compounds of formula (I) include bufeniode, butopamine, denopamine, fenoterol, formoterol, isoxuprine, labetalol, medroxalol, mesuprine, nylidrin, protokylol, ritodrine, salmefamol, sulfinalol.

According to another aspect of the invention the preferred diastereomer or enantiomer of (I) has little or no activity at the a or β adrenoceptors. This activity may be determined by use of the appropriate in vitro assay.

The compounds of formula (I) according to the invention exhibit analgesic activity in animal models. The activity of these compounds may be determined by use of the appropriate *in vivo* assay.

This invention also relates to a method of treatment for patients (including man and/or mammalian animals raised in the dairy, meat or fur industries or as pets) suffering from chronic, acute or neuropathic pain; and more specifically, a method of treatment involving the administration of the analgesic of formula (I) as the active constituent.

Accordingly, the compounds of formula (I) can be used among other things in the treatment of pain conditions such as acute and chronic pain (as well as, but not limited to, pain associated with cancer, surgery, arthritis, dental surgery, trauma, musculo-skeletal injury or disease, visceral diseases) and migraine headache. Additionally the painful conditions can be neuropathic (post-herpetic neuralgia, diabetic neuropathy, drug induced neuropathy, HIV

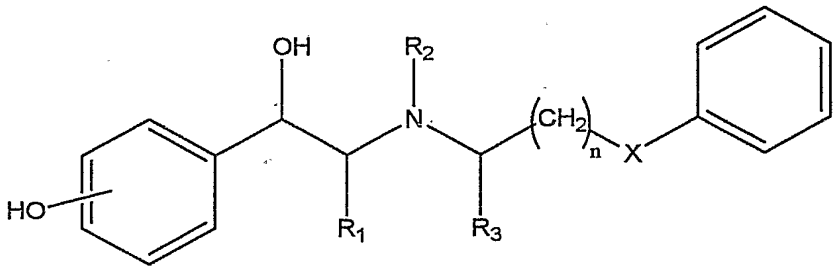
mediated neuropathy, sympathetic reflex dystrophy or causalgia, fibromyalgia, myofacial pain, entrapment neuropathy, phantom limb pain, trigeminal neuralgia. Neuropathic conditions include central pain related to stroke, multiple sclerosis, spinal cord injury, arachnoiditis, neoplasms, syringomyelia, Parkinson's and epilepsia.

It will often be advantageous to use compounds of formula (I) in combination with another drug used for pain therapy. Such another drug may be an opiate or a non-opiate such as baclofen. Especially for the treatment of neuropathic pain, coadministration with gabapentin is preferred. Other compounds that may be used include acetaminophen, a non-steroidal anti-inflammatory drug, a narcotic analgesic, a local anaesthetic, an NMDA antagonist, a neuroleptic agent, an anti-convulsant, an anti-spasmodic, an anti-depressant or a muscle relaxant.

Any suitable route of administration can be used. For example, any of oral, topical, parenteral, ocular, rectal, vaginal, inhalation, buccal, sublingual and intranasal delivery routes may be suitable. The dose of the active agent will depend on the nature and degree of the condition, the age and condition of the patient and other factors known to those skilled in the art. A typical dose is 10-100 mg given one to three times per day.

Claims

1. Use of a compound for the manufacture of a medicament for use in the treatment of a pain condition wherein the compound is of formula I



(I)

wherein

R_1 is H or Me;

R_2 is H or C_{1-6} alkyl or is part of a ring with R_3;

R_3 is H, Me or (when forming part of a ring with R_2) CH_2;

n=0-2;

X is CH_2 or O; and

the two benzene rings are each optionally substituted with OH, OMe, halogen, NHCHO, $NHSO_2Me$, $CONH_2$ or SOMe;

or a salt thereof.

2. Use according to claim 1, wherein the compound is selected from bufeniode, butopamine, denopamine, fenoterol, formoterol, isoxuprine, labetalol, medroxalol, mesuprine, nylidrin, protokylol, ritodrine, salmefamol, and sulfinalol.

3. Use according to claim 1 or claim 2, wherein the pain condition is chronic pain such as chronic back pain, malignant pain, chronic headache (including migraine and cluster headaches) or arthritic pain.

4. Use according to claim 1 or claim 2, wherein the pain condition is acute pain such as post-operative pain, post-traumatic pain or acute disease induced pain.

5. Use according to claim 1 or claim 2, wherein the pain condition is neuropathic pain.

6. Use according to any preceding claim, for use in combination with at least one other agent selected from a non-steroidal anti-inflammatory drug, a narcotic analgesic, a local anaesthetic, an NMDA antagonist, a neuroleptic, an anti-convulsant, an anti-spasmodic, an anti-depressant and a muscle relaxant.